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(54) Title: HIGH DOSE IBANDRONATE FORMULATION

(57) Abstract: The invention relates to a high dose oral formulation of bisphosphonates and to a process for the preparation of such formulations.

High Dose Ibandronate Formulation

The invention relates to a pharmaceutical composition for oral application consisting of a high dose of bisphosphonates or physiologically safe salts thereof as active substance and to a process for the preparation of such compositions.

Aminoalkyl-1,1-diphosphonic acid derivatives (hereinafter called by the general term bisphosphonates) are important pharmaceutical agents in the treatment of bone diseases and some disturbances of calcium metabolism such as hypercalcaemia, osteoporosis, tumour osteolysis, Paget's disease, etc.

Bisphosphonates as pharmaceutical agents are described for example in EP-A-170,228, EP-A-197,478, EP-A-22,751; EP-A-252,504, EP-A- 252,505, EP-A-258,618, EP-A-350,002, EP-A-273,190, WO-A-90/00798 each of which are incorporated herein by reference.

Pharmaceutical forms of currently marketed bisphosphonates are oral formulations (tablets or capsules) or solutions for intravenous injection or infusion. They are systemically well tolerated when administered at therapeutic doses. However, bisphosphonates as a class are irritant to skin and mucous membranes and when given orally on a continuous basis may result in digestive tract side effects, e.g. esophageal adverse events or gastrointestinal disturbances. In consequence, and due to their low oral bioavailability, the oral route of administration has, to date, to follow inconvenient recommendations of use for the patient.

As described, bisphosphonates are accepted as providing strong efficacy in the management of osteoporosis. However, given the administration restrictions related to low oral bioavailability and potential for gastro-intestinal side effects, there is a clear opportunity for regimens which offer improved convenience and flexibility, leading to a higher level of compliance and superior patient management / satisfaction.

Furthermore it has been found in the Ibandronate clinical development program, that Ibandronate showed fracture reduction efficacy with a drug-free interval beyond daily administration. It was quite unexpected that fracture reduction benefit could be derived from a weekly or monthly administration of an oral bisphosphonate with a single or multiple tablet administration scheme.

For this purpose a new composition comprising a high dose, namely up to 250 mg, preferably comprising 150 mg or 100 mg of a bisphosphonate derivative, especially of ibandronate or physiological safe salts thereof had to be prepared, which on the one hand has an increased ratio of active substances vs excipients and on the other hand which fulfills the requirements of stability.

It has been found that the stability of such high dose formulations is substantially increased by adding the disintegrant already in the granulation step together with the active substance and with a part of the filler material. Such compositions are easily dissolvable and have an increased stability on storage both with regard to temperature and humidity.

The pharmaceutical composition according to the invention comprises up to 250 mg, preferably up to 200 mg, especially comprising 150 mg or 100 mg of a bisphosphonate, especially of ibandronate or a physiological safe salt thereof as an active substance.

The following bisphosphonates are active substances which can be used in the pharmaceutical compositions according to the invention in the form of free acids or physiological safe salts or hydrates, particularly sodium salts:
(4-amino-1-hydroxybutylidene)bis-phosphonate (alendronate),
(dichloromethylene)bis-phosphonate (clodronate),
[1-hydroxy-3-(1-pyrrolidinyl)-propylidene]bis-phosphonate (EB-1053),
(1-hydroxyethylidene)bis-phosphonate (etidronate),
[1-hydroxy-3-(methyl pentyl amino)propylidene]bis-phosphonate (ibandronate),
[Cycloheptylamino)-methylene]bis-phosphonate (incadronate),
(6-amino-1-hydroxyhexylidene)bis-phosphonate (neridronate),
[3-(dimethylamino)-1-hydroxypropylidene]bis-phosphonate (olpadronate),
(3-amino-1-hydroxypropylidene)bis-phosphonate (pamidronate),
[1-hydroxy-2-(3-pyridinyl)ethylene]bis-phosphonate (risedronate),
[[(4-chlorophenyl)thiol]-methylene]bis-phosphonate (tiludronate),
[1-hydroxy-2-imidazo-(1,2-a)pyridin-3-yl.ethylidene]bis-phosphonate (YH 529),
[1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis-phosphonate (zoledronate); especially [1-hydroxy-3-(methyl pentyl amino)propylidene]bis-phosphonate (ibandronate)

The said substances and their preparation are known and described, for example, in the following references:

US Patent No. 4,705,651 (Alendronate), US Patent No. 4,927,814 (Ibandronate), US Patents Nos. 3,468,935, 3,400,147, 3,475,486 (Etidronate), O.T. Quimby et al, J. Org. Chem. 32, 4111 (1967) (Clodronate) and US Patent No. 4,505,321 (Risedronate) and US Patents Nos. 4,134,969 and 3,962,432 (Pamidronate), US Patent No. 5,130,304 (EB-1053), US Patent No. 4,970,335 (Incadronate), Belgian Patent No. 885139 (Neridronate), US Patent No. 4,054,598 (Olpadronate), US Patents Nos. 4,746,654, 4,876,248 and 4,980,171 (Tiludronate), US Patent No. 4,990,503 (YH 529) and US Patent No. 4,939,130 (Zoledronate).

Preferred are compositions comprising the equivalent of 150 mg bisphosphonates or physiological safe salts thereof and compositions comprising the equivalent of 100 mg bisphosphonates or physiological safe salts as active substances, respectively. Ibandronate or a physiological safe salt thereof is a particularly preferred active substance, particularly in the form of Na-Ibandronate monohydrate.

The composition further comprises adjuvants such as binders for example polyvinyl-pyrrolidone (e.g. Povidone®) or hydroxypropylmethyl cellulose (e.g. Pharmacoat®), fillers for example lactose in hydrate or anhydrate form, cellulose in microcrystalline or fibrous form (e.g. Avicel®), or starch, disintegrants for example cross-linked polyvinyl pyrrolidone (e.g. Crospovidone® USPNF) or cross carmelose, lubricants for example stearic acid or magnesium stearate, and flow-regulators for example colloidal silicon dioxide.

The preferred form of the composition are tablets preferably coated by a film coating mixture and a plastiziser. Such film coating mixtures and plastizisers are known to the person skilled in the art.

According to the inventions the tablet kernel consists
of 30.0 to 36.0, preferably of .33,3.% of active substance;
of 4.0 to 6.0, preferably of 4.8 to 5.2 % by weight of binder;
of 39.6 to 59.4, preferably of 47.0 to 52.0 % by weight of filler;
of 4.5 to 5.5, preferably of 4.8 to 5.2 % by weight of disintegrant;
of 1.8 to 2.2, preferably of 1.9 to 2.1 % by weight of lubricant; and
of 0.9 to 1.1, preferably of 0.95 to 1.05 % by weight of flow regulator.

Preferably the active substance is ibandronate or a physiological safe alt thereof; preferably the binder is polyvinylpyrrolidone; preferred fillers are lactose in hydrate or anhydrate form, or cellulose in microcrystalline or fibrous form; and a preferred disintegrant is cross-linked polyvinyl pyrrolidone. Preferred are compositions wherein the disintegrant is added

already in the granulate together with the active substance and with a part of the filler material.

Furthermore, the invention relates to a process for the preparation of pharmaceutical compositions for the oral application comprising a high dose of bisphosphonates, especially of ibandronate or a physiological safe salt thereof. According to the invention the pharmaceutical composition is prepared

- by wet granulation of the bisphosphonate or pharmaceutically acceptable salt thereof in the presence of adjuvants such as the binder and a part of fillers mentioned above, characterized in that the disintergrant is added into the granulation mixture;

- fluidising the granulation mixture in a manner known per se;

- subsequently drying the wet granulate and screening the dried granulate through a screen having a suitable mesh width;

- adding the remaining adjuvants such as the fillers, lubricant and flow regulators mentioned above and blending the mixture before processing it by techniques known per se to form pharmaceutical compositions.

In a preferred form of the invention the active substance, a part of the filler, and the disintegrant in dry powder form are granulated by spraying an aqueous binder solution into the powder mixture. The process is preferably carried out at a temperature of 60 to 80 °C, preferably at about 70°C.

The spray granulated material is then dried preferably at a temperature of 60 to 80 °C, preferably at about 70°C and subsequently screened through a fine sieve; the dried granulate is mixed with the remaining amount of the filler, the lubricant, and the flow regulator which were previously passed through a fine sieve. The final blend is then pressed into tablet kernels which are coated with a coating suspension using purified water and a film-coating mixture.

The process according to the invention is carried out as follows:

a) dissolving the binder, preferably Povidone K25® in purified water;

b) charging a drier, preferably a fluid-bed drier with the bisphosphonate, preferably with the mono-sodium salt ($1H_2O$) of Ibandronic acid, a part of the filler preferably with lactose monohydrate and up to 60 % by weight of the total amount of microcrystalline cellulose, and the disintegrant;

c) spray-granulating the raw materials of step b) at a temperature of 60 to 80 °C, preferably at about 70°C with the granulation fluid of step a),

e) drying the spray granulated material of step c) at a temperature of 60 to 80 °C, preferably at about 70°C (setpoint of inlet-air temperature) and subsequently screening the dried intermediate through a fine sieve;

f) mixing the granulate of step e) with the remaining amount of the filler e.g. micro-crystalline cellulose, the lubricant, preferably stearic acid and the flow regulator, for example anhydrous colloidal silica which were previously passed through a fine sieve (e.g. 1mm);

g) compressing the final blend of f) into tablet kernels; and coating the tablet with a coating suspension using purified water and a film-coating mixture comprising for example hypromellose, titanium dioxide and talc (the mixture is purchased from the market e.g. Opadry® 00A28646) and Macrogol 6000®.

The adjuvants are known in the art and are commercially available.

The invention will now be explained in further detail with reference to examples, without being limited thereto.

Example 1:
the preparation of a film coated tablet containing 150 mg active substance is carried out as follows:

1. Dissolve Povidone K25® in purified water.
2. Charge a fluid-bed drier with mono-sodium salt ($1H_2O$) of Ibandronic acid, lactose monohydrate, crospovidone and microcrystalline cellulose. Crospovidone and the microcrystalline cellulose were passed through a fine sieve (e.g. 1mm) before mixing.
3. Spray-granulate the raw materials of step 2 at 70°C (set point of inlet-air temperature) with the granulation fluid of step 1.
4. Perform a final drying of the spray granulated material of step 3 at 70°C (setpoint of inlet-air temperature).
5. Screen the dried intermediate granulate through a fine sieve (e.g. 2mm perforations) and
6. where required, repeat steps 1-5 to obtain the required final batch size.
7. Mix the granulate of step 6 in a container mixer with microcrystalline cellulose, stearic acid and anhydrous colloidal silica. The microcrystalline cellulose, the stearic acid and the anhydrous colloidal silica were passed through a fine sieve (e.g. 1mm) before mixing.

8. Compress the final blend of step 7 into tablet kernels using a rotary tablet press.
9. Prepare the coating suspension using purified water, film-coating mixture comprising hypromellose (60.5%), titanium dioxide (29%) and talc (10.5%); the mixture is purchased from the market (e.g. Opadry® 00A28646) and Macrogol 6000®.
10. Spray the coating suspension of step 9 onto the tablet kernels using a coating unit.

The tablet composition is as follows:

Tablet kernel		
Ibandronic acid	150.0 mg	--
- as mono-sodium salt ($1H_2O$) of Ibandronic acid		168.75 mg
Povidone K25®		22.5 mg
Lactose, monohydrate		162.75 mg
Cellulose, microcrystalline		60.0 mg
Crospovidone		22.5 mg
Stearic acid 95		9.0 mg
Silica, anhydrous colloidal		4.5 mg
Film-coat		
Film-coating mixture *		12.75 mg
Macrogol 6000		2.25 mg

*this film-coating mixture contains: hypromellose (60.5%), titanium dioxide (29%) and talc (10.5%); the mixture is purchased from the market (e.g. Opadry® 00A28646)

The kernel weight is 450 mg and the total tablet weight is 465 mg, the amount of active substance per tablet is equivalent to 150mg of free Ibandronic acid.

Example 1a: for a batch of 110 000 tablets

1. A suitable vessel was charged with 14.850 kg demineralised water and 2.475 kg of Povidone K25® was added under constant stirring. The time of addition was about 15 minutes.
2. A fluid-bed dryer was charged with 18.563 kg ibandronic acid mono sodium salt, 17.903 kg of lactose monohydrate 100, 4.125 kg Avicel PH-102® and 2.475 kg Crospovidone CL®.
3. The components were mixed and spray granulated at a temperature of 70°C with the aqueous solution of Povidone K25® prepared above which was added at 300 g/min with a pressure of 2.5 bar.

4. The granulate was then dried in a fluid-bed dryer at 70°C; and
5. subsequently screened (2.0 mm meshes) to yield 44.540 kg of dried granulated material.
6. 2.426 kg AVICEL PH-102®, 0.970 kg stearic acid and 0.4850 kg silicic acid AEROSIL 200® were screened and added to the dried granulated material (44.650 kg), the components were mixed; and
7. the final blend was compressed into tablets kernels, yield 103 244 kernels.
8. A coating suspension was prepared by dissolving 0.290 kg PEG 6000® (MACROGOL 6000) in 7.743 kg demineralised water and subsequently disperging 1.645 kg OPADRY 00A28646® into this solution.
9. The kernels were coated with the coating suspension under standard conditions.

The tablets have the composition and the weight given in example 1.

Example 2:

the preparation of a film coated tablet containing 100 mg active substance was carried out as described in example 1:

Tablet kernel		
Ibandronic acid	100.0 mg	--
- as mono-sodium salt ($1H_2O$) of Ibandronic acid		112.50 mg
Povidone K25		15.0 mg
Lactose, monohydrate		108.50 mg
Cellulose, microcrystalline		40.0 mg
Crospovidone		15.0 mg
Stearic acid 95		6.0 mg
Silica, anhydrous colloidal		3.0 mg
Film-coat		
Film-coating mixture *		10.20 mg
Macrogol 6000		1.80 mg

*composition as mentioned example 1

The kernel weight is 300 mg and the total tablet weight is 312 mg, the amount of active substance per tablet is equivalent to 100mg of free Ibandronic acid.

Claims

1. A pharmaceutical composition containing as active substance up to 250 mg of bisphosphonates or physiologically safe salts thereof for oral application.

2. A pharmaceutical composition according to claim 1 wherein the tablet kernel consists of
30.0 to 36.0 % of active substance
4.0 to 6.0% by weight of binder;
39.6 to 59.4 by weight of filler;
4.5 to 5.5% by weight of disintegrant;
1.8 to 2.2% by weight of lubricant; and
0.9 to 1.1% by weight of flow regulator.

3. A pharmaceutical composition according to claim 1 or 2, wherein the tablet kernel consists of 33,3.% of active substance;
4.8 to 5.2 % by weight of binder;
47.0 to 52.0 % by weight of filler;
4.8 to 5.2 % by weight of disintegrant;
1.9 to 2.1 % by weight of lubricant; and
0.95 to 1.05 % by weight of flow regulator.

4. A pharmaceutical composition according to claim 1, 2 or 3 comprising the equivalent of 150 mg bisphosphonates or physiologically safe salts as active substance.

5. A pharmaceutical composition according to claim 1, 2 or 3 comprising the equivalent of 100 mg bisphosphonates or physiologically safe salts as active substance.

6. A pharmaceutical composition according to anyone of claims 1, 2, 3, 4 or 5, wherein the active substance is ibandronic acid or physiological safe salts thereof.

7. A pharmaceutical composition containing

Ibandronic acid	100.0 mg	--
- as mono-sodium salt ($1H_2O$) of Ibandronic acid		112.50 mg
Povidone K25®		15.0 mg
Lactose, monohydrate		108.50 mg
Cellulose, microcrystalline		40.0 mg
Crospovidone		15.0 mg
Stearic acid 95		6.0 mg
Silica, anhydrous colloidal		3.0 mg
Film-coat		
Film-coating mixture *		10.20 mg

Macrogol 6000®		1.80 mg

8. A pharmaceutical composition containing

Ibandronic acid	150.0 mg	--
- as mono-sodium salt ($1H_2O$) of Ibandronic acid		168.75 mg
Povidone (K25)		22.5 mg
Lactose, monohydrate		162.75 mg
Cellulose, microcrystalline		60.0 mg
Crospovidone		22.5 mg
Stearic acid 95		9.0 mg
Silica, anhydrous colloidal		4.5 mg
Film-coat		
Film-coating mixture		12.75 mg
Macrogol 6000		2.25 mg

9. A pharmaceutical composition according to anyone of claims 1, 2, 3, 4 or 5, wherein the aminoalkyl-1,1-diphosphonic acid derivative used is alendronate, clodronate, EB-1053, etidronate, ibandronate, incadronate, neridronate, olpadronate, pamidronate, risedronate, tiludronate, YH 529 or zoledronate in the form of the free acid or a pharmaceutically compatible salt or hydrate, particularly the sodium salt.

10. A pharmaceutical composition according to claim 1 to 9, wherein wherein the disintegrant is added in the granulate together with the active substance and with a part of the filler material.

11. A process for the preparation of a composition according to anyone of claims 1 to 10, said process comprising

a) spray-granulating the bisphosphonate, a part of the filler and the disintegrant with a solution of the binder in purified water at a temperature of about 70°C;

b) drying the spray granulated material at a temperature of about 70°C and subsequently screening the dried intermediate through a fine sieve;

c) mixing the granulate with the remaining amount of the filler, the lubricant, and the flow regulator which were previously passed through a fine sieve;

d) compressing the final blend into tablet kernels; and coating the tablet with a coating suspension using purified water and a film-coating mixture.

12. A process according to claim 11, said process comprising

a) dissolving the binder in purified water;

b) charging a drier with the bisphosphonate, a part of the filler, and the disintegrant;

c) spray-granulating the raw materials of step b) at a temperature of about 70°C with the granulation fluid of step a);

e) drying the spray granulated material of step c) at a temperature of about 70°C and subsequently screening the dried intermediate through a fine sieve;

f) mixing the granulate of step e) in a mixer with remaining amount of the filler, the lubricant, and the flow regulator which were previously passed through a fine sieve;

g) compressing the final blend of f) into tablet kernels; and coating the tablet with a coating suspension using purified water and a film-coating mixture.

13. The process according to claim 11 or 12, characterized in that the bisphosphonate is mono-sodium salt ($1H_2O$) of Ibandronic acid.

14. The process according to anyone of claims 11 to 13, characterized in that the disintegrant is crospovidone.

15. A pharmaceutical composition obtainable by the process according to anyone of claims 11 to 14.

16. The invention as described hereinbefore, particularly in examples 1 and 2.

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INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/663 A61K9/20 A61K9/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 6 143 326 A (GABEL ROLF-DIETER ET AL) 7 November 2000 (2000-11-07) claim 1 ---	1,5,6,9 11-15
X	FR 2 727 629 A (SANOFI SA) 7 June 1996 (1996-06-07) example 2 ---	1,9
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
19 November 2003	28/11/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sindel, U

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08732

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HYLDSTRUP L ET AL: "PHARMACOKINETIC EVALUATION OF PAMIDRONATE AFTER ORAL ADMINISTRATION: A STUDY ON DOSE PROPORTINALITY, ABSOLUTE BIOAVAILABILITY, AND EFFECT OF REPEATED ADMINISTRATION" CALCIFIED TISSUE INTERNATIONAL, NEW YORK, NY, US, vol. 53, no. 5, 1993, pages 297-300, XP009009205 ISSN: 0171-967X abstract	1,4,9
X	US 6 294 196 B1 (GABEL ROLF-DIETER ET AL) 25 September 2001 (2001-09-25)	1,2,6,9
Y	examples 3,6	11-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

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